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EXAMINER	
ANDRES, JANET L	
ART UNIT	**PAPER NUMBER**
1649	

DATE MAILED: 09/19/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/441,140	SOLOMON, BEKA	
	Examiner	Art Unit	
	Sharon L. Turner	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *177 and 210-213* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *177 and 210-213* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6-2-06 #1, 6-2-06 #2*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *See Continuation Sheet*.

Continuation of Attachment(s) 6). Other: IDS 8-2-06, 2 PTO-892 listing of references: pp. 1-14 w/o copies of references and pp. 1 with copies of references.

Response to Amendment

1. The file history of 09/441,140 indicates receipt of two IDS transmissions dated 6-2-06 which correspond to the date of the mailing of the Final rejection. Accordingly, it has been determined that this correspondence crossed in the mail and was not available to the Examiner in time for the preparation of the most recent office action. Finality of the previous office action is hereby withdrawn so that the IDS submissions of 6-2-06 may be considered.

2. The after final amendment and IDS of 8-2-06 have been entered and have been fully considered.

3. The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

4. Claims 177 and 210-213 are pending.

5. An telephone interview between Applicant's representative and the Examiner was conducted 7-14-06. The Interview summary was submitted for mailing but did not receive a mail date until 8-1-06. This communication probably had not been received by Applicant as of the filing of the 8-2-06 response. The communication is available by PAIR. If further assistance is required Applicant's should contact the group receptionist or the Examiner. Applicant's notation of the interview and content is noted in the 8-2-06 response at pp. 8-9.

6. Applicant's provide reasoning behind a request to withdrawal finality at pp. 10-11 of the 8-2-06 response. These arguments are moot in view of the reconsideration required for the IDS submission of 6-2-06. As the 8-2-06 response is of record in the file, it too is necessarily considered.

7. Applicant's comments with respect to the submission of the IDS dated 8-22-02 is noted at pp. 12 of the 8-2-06 response. Applicant's comments serve to clarify that the IDS submission of 8-22-02 is of a single page and not 2 pages as indicated, which was the main basis for the confusion. If this is not the case, Applicant's are again encouraged to contact the Examiner.

Reissue Applications

8. Applicant is reminded of the continuing obligation under 37 CFR 1.178(b), to timely apprise the Office of any prior or concurrent proceeding in which Patent No. 5,688,651 is or was involved. These proceedings would include interferences, reissues, reexaminations, and litigation.

Applicant is further reminded of the continuing obligation under 37 CFR 1.56, to timely apprise the Office of any information which is material to patentability of the claims under consideration in this reissue application.

These obligations rest with each individual associated with the filing and prosecution of this application for reissue. See also MPEP §§ 1404, 1442.01 and 1442.04.

Listing of References

9. At p. 13 of the 8-2-06 response, Applicant's assert an obligation by the Examiner to make of record all references considered during the prosecution of the patent.

10. The Examiner thanks Applicant's for their assistance in completion of the PTO-892 listing these references. No copies of the references are supplied to Applicant's as these were provided in the parent file prosecution history. Their listing is for a complete listing of all references considered during the course of prosecution on any patent that may issue as is required in reissue applications.

11. The Examiner acknowledges the reissue oath/declaration filed 8-2-06 which is a supplemental reissue declaration in compliance with both 37 CFR 1.175(b) and 37 CFR 1.175(c).

Rejections Maintained and Necessitated by Amendment

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting

directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

13. Claims 210-211 are rejected under 35 U.S.C. 102(a) as being anticipated by Bickel *et al.* (*Bioconiugate* 5(2): 119-125, March/April 1994) as further evidenced by Solomon, Expert Opin Biol Ther, 2(8):907-917, 2002.

The claims as newly amended encompass therapeutic compositions comprising pharmaceutically acceptable carrier with various antibodies or antigen binding fragments of antibodies noted to provide for the properties of either inhibiting aggregation or maintaining solubility of beta amyloid as recited in the claims, see claims.

Applicants argue in the 1-17-06 response that the Bickel antibody AMY33 is a mouse monoclonal as evidenced in Stern 1989 and accordingly does not anticipate. This argument has been fully considered but is not persuasive. While Stern does evidence that Bickel's AMY33 is a mouse monoclonal this antibody does apply as a genetically engineered monoclonal antibody and it also applies as comprising an antigen binding fragment thereof. As substantially amended the claims are now clearly on point that the monoclonal of the dependent claims applies as a genetically engineered antibody not limited for example to antibodies of chimeric or humanized form. As in the claims, the AMY33 antibody was made to and recognizes human beta amyloid residues 1-28 and as such is an antibody that recognizes and may be obtained using (product by process limitation) residues 1-28. Accordingly, the antibody meets

the structural limitations of the claims. Further as to the inclusion of a pharmaceutically acceptable carrier the antibody is noted in TBS, p. 121, column 1, paragraph 1, for example. It is noted that the reference is silent to the antibodies properties in mediating the functional requirements of (ii), either inhbiting aggregation or maintaining solubility. The PTO does not have sufficient ability to test the antibodies for these inherent properties. Nevertheless, the record does shows that Solomon evidences anti-aggregating or solubility promoting properties to the subject antibodies. Accordingly the burden fairly falls to applicant to evidence otherwise.

Applicant's traverse this rejection together with the rejection below as set forth at pp. 15-16 of the 8-2-06 response. Accordingly, these arguments are also addressed together by the Examiner as set forth below.

14. Claims 210-211 are rejected under 35 U.S.C. 102(b) as being anticipated by Stern *et al. Am J Pathol.*, May 1989, 134(5):973-8 as further evidenced by Solomon, Expert Opin Biol Ther, 2(8):907-917, 2002.

The claims as newly amended encompass therapeutic compositions comprising pharmaceutically acceptable carrier with various antibodies or antigen binding fragments of antibodies noted to provide for the properties of either inhibiting aggregation or maintaining solubility of beta amyloid as recited in the claims.

Stern was not argued separately in the 1-17-06 response, but the comments in response to Bickel are on point that AMY33 is a mouse monoclonal as evidenced in Stern 1989 and accordingly Applicants assert that the reference does not anticipate. This argument has been fully considered but is not persuasive. While Stern does

evidence that AMY33 is a mouse monoclonal, this antibody does apply as a genetically engineered monoclonal antibody and as comprising an antigen binding fragment thereof. Further, Stern is not only on point to AMY33, but is on point to all monoclonals as noted in Table 1 of the reference. All of these antibodies were obtained via immunization with Abeta 1-28 peptide and were shown via ELISA to react specifically to the human beta amyloid BAPP 1-28 epitope. Accordingly these antibodies of Stern also apply as genetically engineered monoclonals or as comprising antigen binding fragments thereof obtained by or reactive to epitiope 1-28. As in the claims, the antibodies were made to and recognize human beta amyloid residues 1-28. Accordingly, the antibodies meet the structural limitations of the claims. Stern *et al.* teaches solutions of the monoclonals in standard ELISA buffer and in immunohistochemistry buffer. As substantially amended the claims are now clearly on point that the monoclonal of the dependent claims applies as a genetically engineered antibody not limited for example to antibodies of chimeric or humanized form. Accordingly, these antibodies meet the structural limitations of the claims. The claims are silent to the functional limitations of (ii) either inhibiting aggregation or maintaining solubility. The PTO does not have sufficient ability to test the antibodies for these inherent properties. Nevertheless, the record shows that Solomon evidences anti-aggregating or soluble promoting properties to the subject antibodies. Accordingly the burden fairly falls to applicant to evidence otherwise.

Applicant's traverse this rejection together with the rejection above as set forth at pp. 15-16 of the 8-2-06 response. In particular Applicant's argue that the claims now

clarify the intent of the term "genetically-engineered antibody" so that it does not read on monoclonals. Support is noted by applicant at column 10, lines 1-3 of the specification. Applicant's also refer to the teachings of Haber noting that techniques for forming genetically-engineered antibodies from monoclonals were well known.

These arguments have been fully considered but are not persuasive. The terms are not defined in any way within the claims. Further, neither Haber nor Applicant's specification at column 10, lines 1-3 serve to provide any definition or structural constraint to the antibodies that preclude the murine monoclonal from the genetically engineered antibody of claims 210 and 211. The process of making monoclonals includes the genetic manipulation of DNA and cells, notably cell fusion techniques. Genetic engineering refers to these recombinant methods, or methods of manipulating DNA or genetic material within a cell, see also citation via the free dictionary by Farlex online;

genetic engineering, the use of various methods to manipulate the DNA (genetic material) of cells to change hereditary traits or produce biological products. The techniques include the use of hybridomas (hybrids of rapidly multiplying cancer cells and of cells that make a desired antibody) to make monoclonal antibodies; gene splicing or recombinant DNA, in which the DNA of a desired gene is inserted into the DNA of a bacterium, which then reproduces itself, yielding more of the desired gene; and, which makes perfect copies of DNA fragments and is used in DNA fingerprinting.

Genetically engineered products include bacteria designed to break down oil slicks and industrial waste products, drugs (human and bovine growth hormones, human insulin, interferon), and plants that are resistant to diseases, insects, and herbicides, that yield fruits or vegetables with desired qualities, or that produce toxins that act as pesticides. Genetic engineering techniques have also been used in the direct genetic alteration of livestock and laboratory animals (see pharming). Genetically engineered products usually require the approval of at least one U.S. government agency, such as the Dept. of Agriculture, the Food and Drug Administration, or the Environmental Protection Agency.

Because genetic engineering involves techniques used to obtain patents on human genes and to create patentable living organisms, it has raised many legal and ethical issues. The safety of releasing into the environment genetically altered organisms that might disrupt ecosystems has also been questioned. The discovery in 2001 of genetically engineered DNA in native Mexican corn varieties made concerns of genetic pollution actual, and led some scientists to worry that the spread of transgenes through cross-pollination could lead to a reduction in genetic diversity in important crops. Imports of genetically modified corn, soybeans, and other crops have been curtailed or limited in some countries, and the vast

majority of such crops are grown in just a handful of nations. The Cartagena Protocol on Biosafety, which has been signed by more than 100 nations and took effect in Sept., 2003, requires detailed information on whether and how imported seeds, plants, animals, other organisms, and the like are genetically modified and permits a nation to bar those imports. The United States, however, is not party to the treaty.

Accordingly, monoclonals are not inconsistent with genetic engineering. Further, the references were previously established as being made by immunization with and being reactive to Abeta 1-28, thereby meeting the claim limitations. Applicant's appear to be construing their claims to be directed to procedures regarding the making of chimeric or humanized antibodies. However, no limitations direct to structures of chimeric or humanized form. Accordingly, rejection is maintained.

15. Claims 210-213 are rejected under 35 U.S.C. 102(b) as being anticipated by Gaskin *et al.*, J Exp Med, 1 April 1993, 177(4):1181-1186 as evidenced by Solomon, Expert Opin Biol Ther, 2(8):907-917, 2002.

Gaskin et al. teach four human monoclonal antibodies, MRE310, 293, 267 and 148 which bind epitope 1-28 of human Aβ and would therefore also be suitably obtained thereby (a product by process limitation). Thus the antibodies of Gaskin meet the structural limitations of the claims (Figure 1; p. 1182). The claims recite functional properties assigned to the claimed antibodies including "inhibits β-amyloid aggregation" and/or "maintains soluble β-amyloid solubility." Although Gaskin *et al.* is silent on said properties, a compound and all of its properties are inseparable; thus, the antibodies are taken to be the same (*In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963)).

Furthermore, the Examiner notes that the antibodies raised against the first 28 amino acids of β-amyloid inherently have "chaperone" or anti-aggregating properties as

evidenced by Solomon, *Expert Opin. Biol. Ther.*, December 2002, 2(8):907-917. Solomon teaches that antibodies targeting the N-terminus of Aβ (residues 1-28) have anti-aggregating properties including solubilization of existing aggregates and inhibition of aggregation (See p. 909). There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of the invention, but only that the subject matter is in fact inherent in the prior art reference [See *Schering v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003)]. The standard antibody solution for performing immuocytochemistry (including ELISA) is PBS which is 1 MM KH2PO4, 3 mM Na2HPO4 8 7H2), pH 7.4, and 155 mM NaCl (see GIBCO Media Formulations from Invitrogen website; retrieved 9/03/2004). Therefore, PBS the standard ELISA solution is almost identical to physiological salt molarity and pH (See Moffett et al. (1993) Human Physiology, 2nd ed., inside cover).
Gaskin *et al.* teach a solution of human monoclonal antibodies in standard ELISA buffer.

Applicant's traverse the rejection as set forth in the response of 1-17-06 at pp. 17-21. In brief, Applicant's argue that the Examiner has not met the burden to establish under inherency that the antibodies and compositions of Gaskin anticipate the rejected claims. Applicant's point to MPEP 2112 for standards of inherency and argue that the Examiner does not establish that the Gaskin antibodies must necessarily "recognize an epitope within residues 1-28 of human beta-amyloid" or "be obtainable using residues 1-28 of human Beta-amyloid," and that such antibodies "maintain the solubility of soluble beta amyloid" or "inhibit aggregation of beta-amyloid," as recited in the claims. Applicants argue that Gaskin at p. 1184 suggests that the epitiope is not within residues

1-28 and is not obtainable using residues 1-28. Further, Applicants suggest that since the antibodies were found in Alzheimer's patients, the reference suggests that these antibodies do not inhibit aggregation or maintain the solubility of soluble beta-amyloid. Applicants further argue that the reference suggests the antibodies are pathogenic, not therapeutic, noting the last paragraph of Gaskin, thus providing no motivation to make a pharmaceutical formulation. Applicant's submit that the claims as newly amended now give weight to the recitation of "a pharmaceutical formulation" and thus distinguish structurally from the prior art as it must be packaged therefore.

Applicant's arguments filed 1-17-06 have been fully considered but are not persuasive. Gaskin does evidence that the antibodies react to Abeta 1-28 and therefore no other proof is needed by the Examiner. That an antibody is reactive to the antigenic epitope to which it binds is a long held art accepted principle and further the recitation that the antibody "may be obtained by" is a product by process limitation not garnering weight where the prior art antibody is already evidenced to provide the recited structural constraints of binding Abeta 1-28. As substantially amended the claims are now clearly on point that the monoclonal of the dependent claims applies as a genetically engineered antibody not limited for example to antibodies of chimeric or humanized form. Accordingly, the Examiners burden has clearly been met via the rejection of record. The fact that the antibody may cross react with other portions or that other portions of a peptide molecule may contribute to epitope stability is immaterial where the antibody is already evidence to bind the requisite epitope. Better binding is not the subject of the claims and mere evidence that certain residues may stabilize such a

binding interaction is not a teaching that negates anticipation where binding is evidenced. Further, as to any intended use, such is not limiting. Also as to motivation, no motivation is required where the reference is anticipatory as herein. The fact that the antibodies are provided in a pharmaceutically acceptable carrier alone is sufficient as disclosed herein. Accordingly, the reference teachings anticipate the claimed invention.

Applicant's traverse this rejection in the 8-2-06 response at pp. 17-18 asserting that none of the antibodies of Gaskin could possibly have been obtained using Abeta 1-28 as an immunogen as Gaskin notes at p. 1184 that there is a contribution from the 29-40 region to the reactive epitope and that the epitope differs from those recognized by xenogeneic antibodies raised against Abeta 1-28.

These arguments have been fully considered but are not persuasive. First, the Examiner notes that the claims are recited in alternative form and that while the claims stipulate that the antibody "is obtainable using residues 1-28 of (human) beta-amyloid as an immunogen," this limitation is not required. The statement is followed by the alternative "or recognizes an epitiope within residues 1-28 of beta-amyloid". This limitation is evidenced as the antibody binds the peptide consisting of Abeta1-28. Accordingly, rejection is maintained for at least these reasons.

Further, the "obtainable" limitation is a product by process limitation and the claim is directed to a composition or product. The product is further noted to be "genetically-engineered," this too approximates a product by process limitation in that no distinguishing structure is conveyed. It is noted as set forth above that this term is inclusive of multiple processes. For example the generic structure of an antibody is

known, but any antibody may be made via different techniques including recombinant production, production in different species of cells and/or organisms, cell fusion techniques and via stimulation with different immunogenic procedures. Academically, an antibody that might be generated via any one technique may be re-producible using any number of others. Accordingly, no evidence supports the conclusion that the Gaskin antibodies cannot be obtained using residues 1-28 of beta amyloid as immunogen. Moreover, the "antibody(ies)" of the claims is a generic recitation, i.e., any number of antibodies exhibiting particular characteristics. The Examiner cannot preclude that the generic antibodies cannot be made (or have not been made) via such other techniques.

Further as to antigen specificity, it is noted that immunization with full length beta-amyloid does in effect "use" (interpreted as open language) Abeta residues 1-28. The claims are not limited to immunization with "a peptide consisting of residues 1-28." Further, while different antibodies may bind with different affinities to the same peptide, or may cross-react with different peptides to different degrees, does not mean that each of them might meet the generic recitations or be made in the same way. The instant antibodies are not precluded from cross-reacting with any other form of beta –amyloid. They are merely required to recognize an epitope within Abeta 1-28. As the antibodies are evidenced to bind this peptide, their characterization is sufficient to fall with in the claim limitations.

The individual characteristics of the genus of antibodies claimed are analyzed as previously set forth. As noted above, a monoclonal antibody may be made via genetic

engineering. Accordingly, the antibodies of Gaskin that are of human monoclonal form at once meet the claim limitations to "a genetically-engineered" antibody and to a "monoclonal" antibody. As previously noted Solomon teaches the importance of the N-termainal 1-28 segment in providing for the solubility characteristics of the full length Abeta peptide and note that antibodies to the N-terminus inhibit aggregation and/or maintain solubility. As the Gaskin antibodies react with this peptide, these properties are deemed to be provided, absent evidence to the contrary. All of the required characteristics of the antibodies are provided, regardless of their means of production, and therefore the reference teachings meet the claim limitations.

16. Claims 210-211 are rejected under 35 U.S.C. 102(a) as being anticipated by Walker *et al.*, *Journal of Neuropathology and Experimental Neurology*, July 1994, 53(4):377-383 as evidenced by Solomon Expert Opin Biol Ther, 2(8):907-917, 2002.

Walker *et al.* teach a monoclonal antibody 10D5, a murine IgG1, kappa light chain (whole IgG and/or Fab fragments) specific for residues 1-16 of Aβ. The reference teaches a pharmaceutical composition of 10D5 in sterile solution, which is administered to rhesus and squirrel monkeys, thus meeting the limitations of the claims with respect to recognizing an epitope within residues 1-28. The reference is not on point to the antibody being obtained by such immunization but such is a product by process limitation not garnering weight against the property already evidenced.

A preamble is not a limitation when the claim is directed to a product and the preamble merely recites a property inherent in an old product defined by the remainder of the claim (See MPEP §2112[R-2]). The claims recite functional properties assigned

to the claimed antibody including "inhibits β-amyloid aggregation" and/or "maintains soluble β-amyloid solubility." However, the 10D5 antibody taught by Walker *et al.* is silent on said properties, a compound and all of its properties are inseparable. The antibodies are taken to be the same (*In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963)). Furthermore, the Examiner notes that the antibodies raised against the first 28 amino acids of β-amyloid inherently have "chaperone" or anti-aggregating properties as evidenced by Solomon, *Expert Opin. Biol. Ther.*, December 2002, 2(8):907-917. Solomon teaches that antibodies targeting the N-terminus of Aβ (residues 1-28) have anti-aggregating properties including solubilization of existing aggregates and inhibition of aggregation (See p. 909). There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of the invention, but only that the subject matter is in fact inherent in the prior art reference [See *Schering v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003)]. Walker *et al.* teach a solution of the monoclonal antibodies in sterile saline solution. Accordingly, the reference teachings anticipate the claimed invention.

Applicants argue in the 1-17-06 response that the rejection is obviated as the claims are directed to human antibodies and to genetically engineered antibodies and thus the reference fails to anticipate.

These arguments have been fully considered but are not persuasive. As amended the claims are directed to therapeutic compositions comprising pharmaceutically acceptable carrier with various antibodies or antigen binding

fragments of antibodies noted to be human or genetically engineered, and to provide for the properties of either inhibiting aggregation or maintaining solubility of beta amyloid as recited in the claims, see claims. It appears that Applicant's opinion is that monoclonals are not genetically engineered. However the artisan recognizes that the process of making monoclonals is the result of genetic engineering. As substantially amended the claims are now clearly on point that the monoclonal of the dependent claims applies as a genetically engineered antibody not limited for example to antibodies of chimeric or humanized form. It is not clear how the two may be separated and nonetheless the mouse monoclonal comprises the antigen binding fragment. Therefore anticipation is provided to the monoclonals that are genetically engineered and not limited to human.

Applicants traverse the rejection in the 8-2-06 response at pp. 18-19. In particular, Applicants argue that the claims specify that the genetically-engineered antibodies are obtained from monoclonal antibodies.

This argument has been fully considered but is not persuasive. As noted above, monoclonals are genetically engineered. Accordingly, this claim limitation is met.

17. Claims 210-213 and 177 are rejected under 35 U.S.C. 102(e) as being anticipated by Anderson et al., US 5,589,154 issued 12-21-1996 as evidenced by Solomon, Expert Opin Biol Ther, 2(8):907-917, 2002.

Anderson teaches administration of antibodies that bind beta-amyloid, particularly beta-amyloid residues 1-28 for the treatment and prevention of vascular hemorrhaging and Alzheimer's disease. Solomon teaches that antibodies targeting the

N-terminus of Aβ (residues 1-28) have anti-aggregating properties including solubilization of existing aggregates and inhibition of aggregation (See p. 909). Anderson also teaches such administration for diagnosis or labeling in vivo. The antibodies noted are characterized as obtainable using Abeta 1-28 antigen, the antibodies are of human and monoclonal form and include antibodies that are modified to become human i.e., are of chimeric or humanized form, generated via recombinant genetic engineering. Further, the antibodies may be of single chain form. The antibodies are included in pharmaceutical composition and are provided with a pharmaceutically effective carrier. The direct excerpts from the patent are appended below.

> Detailed Description Text (22):
> The preferred binding agents of the present invention are antibodies or antibody fragments. Such antibodies may be intact immunoglobulins, or may be antibody fragments (F(ab'), F(ab').sub.2, single chain antibodies, etc.), recombinant antibodies, antibody fusion proteins, chimeric antibodies, etc. Such molecules may be obtained by screening among antibodies elicited in response to immunization with either a .beta. amyloid peptide or a peptide or peptidomimetic molecule that is a "functional analog" of a .beta.-amyloid peptide.
> Detailed Description Text (24):
> The amino acid sequence of the .beta./A4 amyloid peptide is shown as SEQ ID NO:1. Preferred biologically active fragments of the .beta./A4 amyloid peptide lack amino acid residues 29-42 of SEQ ID NO:1. The fragments may be composed of only those amino acid residues present in SEQ ID NO:1, or may contain deletions, insertions, additions or substitutions of one, two or more amino acids from either terminus, or from an internal site. Examples of such fragments include a peptide comprising SEQ ID NO:1 residues 1-28, and a peptide comprising SEQ ID NO:1 residues 1-28, wherein the amino acid at residue 22 (Glu) is replaced with Gln.
> Detailed Description Text (35):
> In a highly preferred embodiment, populations of polyclonal .beta.-amyloid peptide antibodies, or species of monoclonal .beta.-amyloid peptide antibodies, are further screened to remove those antibodies that are additionally capable of specifically binding to fibrin. In the case of polyclonal sera, such removal can readily be accomplished by passing the sera through a column containing immobilized fibrin. In the case of monoclonal antibodies, such removal can be accomplished by evaluating the capacity of the molecule to bind fibrin, and then discarding those hybridomas that produce antibodies that specifically bind both .beta.-amyloid peptide and fibrin. The elimination of antibodies that bind fibrin serves to ensure that the antibodies will not disrupt the desired ability of the administered t-PA to dissolve fibrin clots.
> Detailed Description Text (36):
> Where chronic or prolonged administration is desired, the use of non-immunogenic antibodies is preferred. Such molecules can be pseudo-homologous (i.e., produced by a non-human species, but altered to a form that is immunologically indistinct from human antibodies). Examples of such

pseudo-homologous molecules include "humanized" (i.e., non-immunogenic in a human) antibodies prepared by recombinant or other technology. Such antibodies are the equivalents of the monoclonal and polyclonal antibodies, but are less immunogenic, and are better tolerated by the patient.
Detailed Description Text (62):
The above-described therapeutic agents of the present invention can be formulated according to known methods used to prepare pharmaceutically useful compositions, whereby these materials, or their functional derivatives, are combined in admixture with a pharmaceutically acceptable carrier vehicle. Suitable vehicles and their formulation, inclusive of other human proteins, e.g., human serum albumin, are described, for example, in Remington's Pharmaceutical Sciences (16th ed., Osol, A., Ed., Mack, Easton PA (1980)). In order to form a pharmaceutically acceptable composition suitable for effective administration, such compositions will contain an effective amount of such agents, together with a suitable amount of carrier vehicle.

Accordingly, the claim limitations are fairly anticipated.

18. Claims 210-211 are rejected under 35 U.S.C. 102(e) as being anticipated by Suzuki et al., US 5,750,349 issued 5-12-1998 as evidenced by Solomon, Expert Opin Biol Ther, 2(8):907-917, 2002.

Suzuki et al., teach mouse hybridomas producing murine monoclonal antibodies generated to and that bind specific portions of beta-amyloid, particularly N-terminal, 1-16. As the immunogen is wholly within residues 1-28 the antibody produced thereby would recognize an epitiope within residues 1-28. Solomon teaches that antibodies targeting the N-terminus of Aβ 1-28 (specifically containing the EFRH epitope of amino acids 3-6) have anti-aggregating properties including solubilization of existing aggregates and inhibition of aggregation (See p. 909). The antibodies are included in pharmaceutical composition and are provided with a pharmaceutically effective carrier. As noted above, monoclonals are genetically engineered, see for example cell fusion. Accordingly, the reference teachings anticipate the claimed invention. The direct excerpts from the patent are appended below.

Brief Summary Text (15):
More particularly, the present inventors have prepared a plurality of monoclonal antibodies using .beta.-amyloid (25-35), .beta.-amyloid (35-43), .beta.-amyloid (1-40) and .beta.-amyloid (1-16) as

immunogens. By combination of the antibodies, the present inventors developed an immunoassay by which .beta.-amyloids or derivatives thereof can be detected with high sensitivity and specificity without cross reaction with .beta.-amyloid (1-28). Namely, using .beta.-amyloid (25-35), .beta.-amyloid (35-43) and .beta.-amyloid (1-40) as immunogens, the present inventors have established monoclonal antibodies which recognize C-terminal portions of .beta.-amyloids or derivatives thereof, for example, antibodies designated BA-27a, BS-85a and BC-05a. Of these, BS-85a and BA-27a each only show an extremely low affinity for the .beta.-amyloids in a competitive immunoassay using labeled .beta.-amyloids. Nevertheless, studies have revealed that combinations of them with two kinds of antibodies selected from monoclonal antibodies to an N-terminal portion (.beta.-amyloid (1-16)) of the .beta.-amyloids, namely antibodies designated BAN-052a and BAN-50a, can provide a sandwich immunoassay with extremely high sensitivity to the .beta.-amyloids. Further, the present inventors have shown that a sandwich immunoassay in which BC-05a is combined with BAN-50a detects the .beta.-amyloids with high sensitivity in a formic acid extract from the brain of a patient with Alzheimer's disease without cross reaction with .beta.-amyloid (1-40). Furthermore, the present inventors have established monoclonal antibodies which recognize partial peptides in central portions of .beta.-amyloids or derivatives thereof, for example, the antibody designated BP-90a.
Brief Summary Text (193):
Further, as the monoclonal antibodies recognizing the partial peptide in the central portion of the .beta.-amyloid which are used in the sandwich immunoassays of the present invention, antibodies prepared using .beta.-amyloid (18-28) represented by SEQ ID NO:12 as the immunogen are suitably used. The present inventors prepared nine kinds of hybridomas producing these antibodies. In particular, monoclonal antibodies BP-01a, BP-02a, BP-03a and BP-90a produced from four hybridomas BP-01, BP-02, BP-03 and BP-90 are suitable, and BP-03a and BP-90a can also recognize .beta.-amyloid (17-28) represented by SEQ ID NO:11. Of these monoclonal antibodies, BP-90a is particularly suitable.
Detailed Description Text (85):
Each of the monoclonal antibodies was purified from the resulting ascites with a Protein-A column. That is, 6 to 20 ml of the ascites was diluted with the same amount of binding buffer (1.5M glycine containing 3.5M NaCl and 0.05% NaN.sub.3, pH 9.0), and then subjected to a recombinant protein-A-agarose (Repligen) column previously equilibrated with the binding buffer to elute the specific antibody with elution buffer (0.1M citrate buffer containing 0.05% NaN.sub.3, pH 3.0). The eluate was dialyzed against PBS at 4.degree. C. for 2 days, followed by sterile filtration with a 0.22-.mu.m filter (Millipore). The purified solution was stored at 4.degree. C. or -80.degree. C.

Claim Rejections - 35 USC § 103

19. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

20. Claims 212-213 and 177 are rejected under 35 U.S.C. 103(a) as obvious over either Bickel *et al., Bioconiugate* 5(2): 119-125, March/April 1994 or Stern et al., *Am J Pathol.*, May 1989, 134(5):973-8, in view of Becker *et al.*, European patent application, EP 0613007 A2 and Anderson et al., US 5,589,154 issued 12-21-1996.

Bickel et al., and Stern et al., each teach antibody and composition of the requisite epitope specificity as set forth above, specifically preferred antibody AMY33 recognizing Abeta 1-28.

The Bickel and Stern antibody is not a human monoclonal (claim 212-213) or single chain (claim 177).

Becker *et al.* teach pharmaceutical formulations containing antibodies having specificity for β-amyloid peptide. The reference teaches antibodies and fragments of antibodies, including chimeric, humanized, veneered, resurfaced or CDR-grafted antibodies, single-chain antibodies as well as human monoclonal antibodies and genetically engineered monoclonal antibodies (p. 4 columns 5-6). These antibodies ar

noted to be of a preferred form for reduction of hyperimmunogenicity in vivo for example when used for treatment or for detection of amyloid plaques.

Anderson et al., also teach administration of Abeta antibodies 1-28 of human, humanized and of single chain monoclonal form for treatment of vascular hemorrhaging and Alzheimer's disease and for diagnosis and labeling of amyloid plaques in vivo.

Accordingly, the artisan would be motivated by Becker and Anderson to modify the Bickel or Stern antibody with the requisite epitope specificity to human, humanized or single chain form for in vivo administration, detection and diagnosis of disease or for treatment as taught by either Becker or Anderson with reduced hyperimmunogenicity in vivo. The preferred epitope specificity is provided by the AMY33 species.

21. Claim 177 is rejected under 35 U.S.C. 103(a) as obvious over Gaskin *et al.*, *J Exp Med*, 1 April 1993, 177(4):1181-1186 in view of Becker *et al.*, European patent application, EP 0613007 A2 and Anderson et al., US 5,589,154 issued 12-21-1996.

Gaskin et al., teach human monoclonal antibody and composition of the requisite epitope specificity as set forth above reacting with Abeta 1-28, specifically MRE310, 293, 267 and 148.

The Gaskin antibody is not single chain (177).

Becker *et al.* teach pharmaceutical formulations containing antibodies having specificity for β-amyloid peptide. The reference teaches antibodies and fragments of antibodies, including chimeric, humanized, veneered, resurfaced or CDR-grafted antibodies, single-chain antibodies as well as human monoclonal antibodies and genetically engineered monoclonal antibodies (p. 4 columns 5-6). These antibodies are

noted to be of a preferred form for reduction of hyperimmunogenicity in vivo for example when used for treatment or for detection of amyloid plaques.

Anderson et al., also teach administration of Abeta antibodies 1-28 of human, humanized and of single chain monoclonal form for treatment of vascular hemorrhaging and Alzheimer's disease and for diagnosis and labeling of amyloid plaques in vivo.

Accordingly, the artisan would be motivated by Becker and Anderson to modify the Gaskin antibody with the requisite epitope specificity to single chain form for in vivo administration, detection and diagnosis of disease or for treatment as taught by either Becker or Anderson with reduced hyperimmunogenicity in vivo.

22. Claims 212-213 and 177 are rejected under 35 U.S.C. 103(a) as obvious over Walker *et al.*, *Journal of Neuropathology and Experimental Neurology*, July 1994, 53(4):377-383, in view of Becker *et al.*, European patent application, EP 0613007 A2 and Anderson et al., US 5,589,154 issued 12-21-1996.

Walker et al., each teach antibody and composition of the requisite epitope specificity as set forth above, specifically preferred antibody 10D5 to epitiope 1-16, including anti-aggregating epitiope of amino acids 3-6 and reactive with epitiope within Abeta 1-28.

The Walker antibody is not a human monoclonal (claim 212-213) or single chain (claim 177).

Becker *et al.* teach pharmaceutical formulations containing antibodies having specificity for β-amyloid peptide. The reference teaches antibodies and fragments of antibodies, including chimeric, humanized, veneered, resurfaced or CDR-grafted

antibodies, single-chain antibodies as well as human monoclonal antibodies and genetically engineered monoclonal antibodies (p. 4 columns 5-6). These antibodies are noted to be of a preferred form for reduction of hyperimmunogenicity in vivo for example when used for treatment or for detection of amyloid plaques.

Anderson et al., also teach administration of Abeta antibodies 1-28 of human, humanized and of single chain monoclonal form for treatment of vascular hemorrhaging and Alzheimer's disease and for diagnosis and labeling of amyloid plaques in vivo.

Accordingly, the artisan would be motivated by Becker and Anderson to modify the Walker antibody with the requisite epitope specificity to human, humanized or single chain form for in vivo administration, detection and diagnosis of disease or for treatment as taught by either Becker or Anderson with reduced hyperimmunogenicity in vivo. The preferred epitope specificity is provided by the 10D5 species.

23. Claims 212-213 and 177 are rejected under 35 U.S.C. 103(a) as obvious over Suzuki et al., US 5,750,349, in view of Becker *et al.*, European patent application, EP 0613007 A2 and Anderson et al., US 5,589,154 issued 12-21-1996.

Suzuki et al., each teach antibody and composition of the requisite epitope specificity as set forth above, specifically preferred antibody to epitiope 1-16, including anti-aggregating epitiope of amino acids 3-6 and reactive with epitiope within Abeta 1-28, see in particular BAN-50a and BAN-052a.

The Suzuki antibodies are not human monoclonals (claim 212-213) or single chain (claim 177).

Becker *et al.* teach pharmaceutical formulations containing antibodies having specificity for β-amyloid peptide. The reference teaches antibodies and fragments of antibodies, including chimeric, humanized, veneered, resurfaced or CDR-grafted antibodies, single-chain antibodies as well as human monoclonal antibodies and genetically engineered monoclonal antibodies (p. 4 columns 5-6). These antibodies are noted to be of a preferred form for reduction of hyperimmunogenicity in vivo for example when used for treatment or for detection of amyloid plaques.

Anderson et al., also teach administration of Abeta antibodies 1-28 of human, humanized and of single chain monoclonal form for treatment of vascular hemorrhaging and Alzheimer's disease and for diagnosis and labeling of amyloid plaques in vivo.

Accordingly, the artisan would be motivated by Becker and Anderson to modify the Suzuki antibody with the requisite epitope specificity to human, humanized or single chain form for in vivo administration, detection and diagnosis of disease or for treatment as taught by either Becker or Anderson with reduced hyperimmunogenicity in vivo. The preferred epitope specificity is provided by the BAN-05a or –052a species.

Conclusion

24. No claims are allowed.

25. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is (571) 272-0894. The examiner can normally be reached on Monday-Thursday from 7:00 AM to 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached at (571) 272-0867.

Sharon L. Turner, Ph.D.
September 6, 2006

SHARON TURNER, PH.D.
PRIMARY EXAMINER
9-6-06